REVIEW ARTICLE

Therapeutic efficacy of Nanosponges in novel drug delivery: recent advantages and applications

Shah Esha Bhavin

Bhavin S.E. Therapeutic efficacy of Nanosponges in novel drug delivery: recent advantages and applications. J Nanosci Nanomed 2022;6(5): 01-07.

ABSTRACT

Nanotechnology and miniaturization have been a huge boon to the field of novel drug delivery and have revolutionized the possibilities in the modern-day healthcare sector. The design of nano-scale drug carriers using various nanotechnology-based approaches for the delivery of lipophilic drug molecules is the current trend in novel drug delivery-based research. Hence the study on nanotech-based approaches along with their advantages and applications for solubility and bioavailability enhancement of poorly soluble potent drug molecules is indeed promising. Nanosponges (NSs) are nanotechnology-based drug carriers which are encapsulating type of vehicles that host both lipophilic and hydrophilic drugs/substances. They are prepared using a biodegradable polymer and a cross linker in a specified ratio and compose a cavity which can house lipophilic or hydrophilic drug molecules. An elaborate literature review and patent search stresses on the promising applications and advantages of nanosponges in modern day novel drug delivery. Substances like lipophilic drug molecules, nutraceuticals, gases, proteins and peptides, volatile oils, genetic material, etc. can be loaded on these nano-carriers., which are stable, compact, convenient to synthesize and easy to scale-up in laboratory. This review stresses on the advantages and applications of cyclodextrin based NS in novel drug delivery and throws light on some information on the patented work in this area. Various nanosponge formulations such as parenteral, topical, oral or inhalation are showing promising results in the healthcare domain and have tremendous potential for future growth and research. Therefore, due to their propitious advantages and applications in modern day novel drug delivery, NSs having tremendous potential to create a breakthrough in the healthcare domain. The authors of the review hope that this elaborate and updated review on advantages and applications of NSs in novel drug delivery discussed here could significantly help the researchers and scientists gain useful information and substantial insight about NS in novel drug delivery applications.

Key Words: *Novel drug delivery; Nanosponges; Cyclodextrin; Nanocarrier; Nanotechnology; Bioavailability*

INTRODUCTION

The healthcare domain is a gigantic research platform and the emerging trends and approaches in the modern-day medicine are growing by leaps and bounds. The range of systems and approaches that can be used to deliver therapeutics is growing and advancing at an incredible rate and Nanotechnology is a blessing to these! The transformation of a molecule having solubility and bioavailability issues and significantly improving its performance characteristics in terms of stability, safety, efficacy and bioaccessibility is what a novel drug delivery approach is all about [1]. In a nutshell, NDDS is a new approach to drug delivery that is novel and overcomes the limitations of conventional drug delivery approaches and offers significant advantages [2].

Nanotechnology is a field in research and innovation which involves the concept of 'miniaturization' and offers paramount applications in the field of therapeutics, diagnosis and research in the healthcare domain [3]. Nanotechnology offers drugs in the nanometer size range, which enhances the performance in a variety of dosage forms. Various advantages of nano-sizing are decreased fed/fasted variability, decreased patient-to-patient variability, enhanced solubility, increased oral bioavailability, increased rate of dissolution, increased surface area, less amount of dose requirement and more rapid onset of therapeutic action [4].

Examples of different types of nanocarriers are polymeric or solid lipid nanoparticles, lipid or albumin nanocapsules, liposomes and micelles, dendrimers, nanovesicles, nanogels, nano-emulsions, and nanosuspensions. Nanocarriers are important components in novel drug formulation [5]. They increase bioavailability, protect and stabilize more sensitive agents (e.g., proteins), minimize side effects and provide means for active targeting [6]. Nanocarriers for drugs are commonly composed of an outer polymer shell and inner core for drug carriage [7]. The outer core imparts stability, determines particle circulation time, and defines the interaction of the nanoparticle with the surrounding environment and cell surfaces [8]. These are typically 1 nm to 300 nm in size and loaded with a therapeutically active agent. Various novel approaches like hydrophilic nanogels, solid lipid nanoparticles, and NSs applied very recently in the delivery of poorly soluble drugs, prolonging the residence time, minimize side effects and, thereby enhancing, bioavailability and therapeutic efficacy of the drugs [9].

Pharmaceuticals designed using nanotechnology cover a variety of nanobiomaterials and nano-size drug delivery systems like nanoparticles, nanocrystals, nanoemulsions, nanoconjugates, liposomes, dendrimers, nanogels, nanocapsules, lipid nanospheres etc. Such nanopharmaceuticals have shown promising benefits to increase the surface area per unit volume, enhanced aqueous solubility, target specificity, controlled release potential, biocompatibility, precise control of particle size and ability for drug combination therapy [10]. Nanopharmaceuticals have made notable impact in principal areas like cancer, Central Nervous System (CNS) disorders, cardiovascular diseases, diabetes, orthopaedic diseases, immunological disorders and infection control [11].

LITERATURE REVIEW

Fundamentals of nanotechnology approach in novel drug delivery

Nanomedicine is the branch of medicine that utilizes the science of nanotechnology in the determent and cure of various diseases using the nanoscale materials, like biocompatible nanoparticles and nanorobots, for various applications including, diagnosis, delivery or sensory purposes in a living organism [12]. Drugs with compromised solubility possess various biopharmaceutical delivery issues including limited bio-accessibility after intake through mouth, less diffusion capacity into the outer membrane, require more quantity for intravenous intake and unwanted toxicity issues. However, all these limitations could be overcome by the application of nanotechnology-based approaches in the drug delivery mechanism which has been a boon and has definitely brought a paradigm shift in the field of novel drug delivery [13].

Different novel carrier-based drug delivery systems

The main transporting tool for carrying the molecules/dugs for

Krishna School of Pharmacy and Research, Krishna Edu Campus, Vadodara, Gujarat, India

Correspondence: Shah Esha Bhavin, Krishna School of Pharmacy and Research, Krishna Edu Campus, Vadodara, Gujarat, India, E-mail: eshuu13@gmail.com *Received: 19-Sep-2022, Manuscript No. PULJNN-22-5781; Editor assigned: 21-Sep-2022, Pre QC No. PULJNN-22-5781 (PQ); Reviewed: 22-Sep-2022, QC No. PULJNN-22-5781 (Q); Revised: 25-Sep-2022, Manuscript No. PULJNN-22-5781 (R); Published: 30-Sep-2022, DOI: 10.37532/puljnn.2022.6(5).1-7.*

pharmaceutical, cosmetic or nutraceutical applications are defined as drug carriers. They are biocompatible and have tremendous scope for industrial and scientific interests [14]. The application of nanotechnology for drug delivery provides scope for advantageous treatments with targeted delivery and reduced side effects [15]. Nanotechnology drug delivery applications occur through the use of carefully designed nanomaterials as well as forming delivery systems from nanoscale molecules. The highlight of nanotechnology aided drug delivery is that it offers drugs in the nanometer size range, which increases the performance in a variety of dosage forms [16]. The myriad of advantages that nano-sizing offers are enhanced solubility, oral bioavailability, increased surface area and targeted drug release. Nanopharmaceuticals have revolutionized drug delivery and the total medical and pharmaceutical domain. With the advent of nanopharmaceuticals, pharmaceutical nanotechnology and novel drug delivery have had a notable impact on disease prevention to provide in-depth knowledge into the molecular crux of diseases and are useful diagnostic and therapeutic markers. Modern day novel drug delivery systems function due to nanocarriers like nanogels, polymeric or solid lipid nanoparticles, lipid or albumin nanocapsules, micelles, liposomes, dendrimers, nanovesicles, nanoemulsions and nanosuspensions, that are its important pillars. They enhance bioavailability, protect and stabilize sensitive agents (e.g. proteins), minimize side effects and promote active targeting. Nanotechnology aided nanocarriers comprise of an outer shell made of polymeric material and an inner dent for drug carriage. Imparting stability, determination of particle circulation time, the interaction of the nanoparticle with its surrounding environment and cell surfaces is determined by the outer core [17,18]. Nanocarriers, which are generally sized between 1 nm-500 nm and stacked with therapeutically active molecules provide an array of opportunities for developing drug delivery strategies. Various novel approaches are explored recently in a plethora of applications like taste masking, delivery of insoluble actives, prolonging the retention time, reducing side effects and, thereby enhancing bioaccesibility and therapeutic efficacy of the drugs. Figure 1 illustrates different novel carrier-based drug delivery systems.

CYCLODEXTRIN BASED NANOSPONGES

NS are defined as novel class of encapsulating type of drug delivery system, which enmesh the drug within its core [18]. Based on their association with the drug molecules, these nanoparticles may be conjugating, encapsulating or complexing in nature. They clearly represent a three-dimensional structure or a scaffold. The globular structure is formed by the 'crossover' segments of the polyester, by forming bonds between its adjacent chains that possess various cavities wherein drug molecules can be housed. The advantages include increased surface area, stability and negative zeta potential. The poor aqueous solubility, unsatisfactory pharmacokinetic properties, and problem of bioavailability associated with novel drugs portray numerous obstacles in the formulation of conventional dosage forms like tablets, capsules, suspensions, emulsions, etc. NSs are a capable of encapsulating or entrapping both lipophilic and hydrophilic drugs [19]. Target-specific drug delivery and controlled drug release are the advantages offered by NSs which make them a promising carrier for novel drug delivery system. In the near future, NS-based products will capture a huge market for commercialization due to their improved properties and promising advantages [20]. They are effective vehicles for targeted drug delivery, by overcoming the issues related to poor availability and toxicity, due to their ability to amalgamate water soluble and water insoluble drug into their cavities [21]. They care synthesized by mixing a polymer and cross linker in a specified molar ratio. Generally, the polymer used is cyclodextrin molecule.

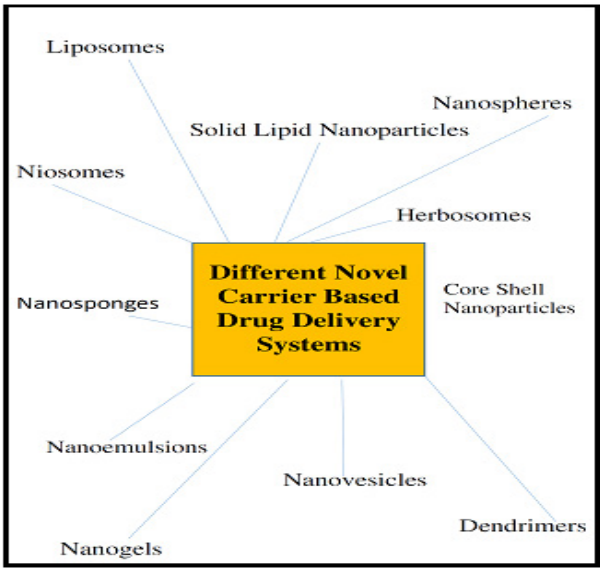

Figure 1) *Different novel carrier based drug delivery systems*

Cyclodextrins are biodegradable biological entities of cyclic oligosaccharides, contain α-1,4 linked cyclic glucopyranose oligomers which are prepared by enzymatic action on starch. Their molecular structure depicts a truncated cone or inverted bucket, consisting of a hydrophilic external surface and a nonpolar interior core. α, β and γ is the main functional moiety of cyclodextrins consisting of six, seven and eight glucopyranose blocks respectively. Additional applications in pharmaceuticals include warding off drug–drug interactions, offering programmable release, converting lipophilic drugs into microcrystalline powders, diminishing ocular and gastrointestinal irritation, and turn down unpleasant taste and smell [22]. This genre of drug delivery offers a propitious platform in the use of nanomedicine for targeted drug delivery. NS adhere to the target site and stick to it to offer drug release in a predictable manner as they are synthesized by treating cyclodextrins, in a particular ratio, with suitable crosslinking agents. Owing to their higher drug loading capacity, they are favorable in formulation design for bypassing the stability, solubility and delayed release of actives related issues [23]. The delivery of proteins, enzymes and vaccines is challenging due to their stability issues that can be overcome by NS approach. They can administer the drugs through a variety of routes like oral, transdermal topical, parenteral, etc. An active carbonyl compound, e.g., carbonyldiimidazole, triphosgene, diphenyl carbonate, or organic dianhydrides provide promising results as drug carriers as per literature survey [24]. The net effect is formation of spherical particles with hydrophobic cavities and hydrophilic channels where drug molecules can be entrapped. A single NS system consists of a myriad of interconnecting voids within a non-collapsible structure capable of holding a wide variety of substances. Cyclodextrin based NS are spherical in shape, having a negative surface charge and sizes in the range of 200 nm-500 nm [25].

Synthesis of nanosponges

The NSs are novel versatile nanocarriers which are synthesized from a solvent method or melt method [26]. The methods include Melt method, Solvent method, Ultrasound assisted synthesis and microwave assisted synthesis [27]. Of these methods, Ultrasound assisted synthesis method is widely adopted as it is desirable on lab scale and also solvent free. Broadly summarizing, the synthesis procedure involves mixing the polymer with a cross linking agent, which dramatically modulates the dimensions of the cavity to a desired size to encapsulate the drug molecule [28]. The final product is a nanoparticulate solid with a spherical morphology which acquires enhanced solubalisaton potential [29]. Figure 2 illustrates the different methods for the synthesis of nanosponges.

Characterization of nanosponges

To understand and study the interaction of NSs with loaded drugs and their synthetic procedures, design and fabrication, NSs are characterized by parameters like phase solubility studies, porosity, solid state interaction study, FTIR, Zeta Potential, SEM and TEM, Differential scanning calorimetry,

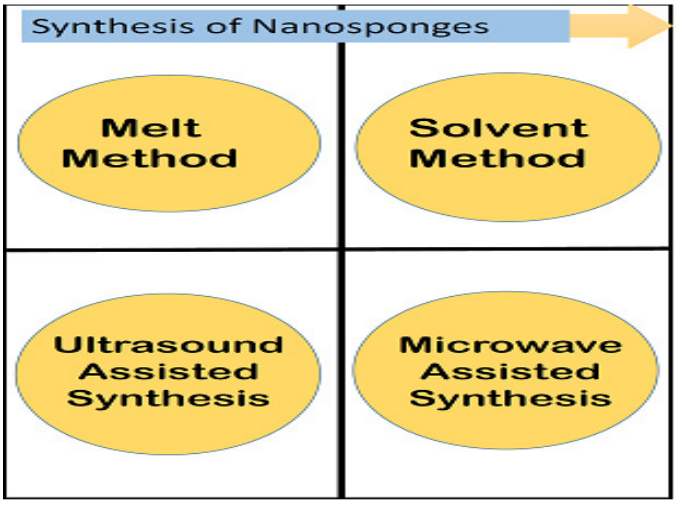

Figure 2) *Different methods for the synthesis of nanosponges*

X-Ray diffraction study etc. [30].

Advantages of nanosponges

1. They are versatile nanocarriers capable of carrying both hydrophilic and lipophilic drug molecules which are easy to handle and store.
2. The promising feature of NSs is that the scientists and researchers can control the dimensions of their cavity as per need and they can be produced in a range of dimensions from 1 µm or less.
3. Desired sizes and dimensions can be prepared by properly controlling the polymer: Cross linker ratio.
4. Synthesis by certain method (eg. Ultrasound assisted method, Melt Method) is solvent free approach.
5. Beta cyclodextrin used as a polymer is biodegradable in nature, thus this approach is environment friendly.
6. The crystal structure of NS determines their efficiency in drug loading. Paracrystalline forms show different drug loading capacities while higher degree of drug loading is witnessed in crystalline forms.
7. NSs retain stability at high temperatures and show negligible solubility in organic solvents.
8. They provide multiple cavities for drug loading. They are non-toxic, and pervious in nature.
9. NSs exhibit stability in a wide pH range from 1-11 and are spherical in shape with high surface area.
10. They form clear opalescent suspension in water.
11. Tailored release profile and suitable capture and transport of drug molecules is witnessed due to the three-dimensional network like structure of NS.
12. NS are capable nanocarriers for solubility enhancement, taste making and offering shieling to drug.
13. Various nutraceutical molecules, natural products, enzymes, proteins, peptides, vaccines etc. can be easily enmeshed in their cavity.
14. Additionally, they show a promising scope for incorporating small molecules, macromolecules, ions and gases within their structure.
15. They can be easily formulated into a variety of dosage forms like tablet, capsules and dry suspensions.
16. These versatile novel carriers have become an interesting ray of hope for the present day nutraceutical, cosmeceutical and biotech industries in addition to pharmaceuticals.
17. NS bind to targeted site with the help of crosslinkers and hence are desired nanocarriers for targeted drug delivery.
18. Synthesis and characterization of NS is possible on lab scale.

Advantages and applications of nanosponge approach in novel drug delivery

NS prepared from cyclodextrins are considered to be spherical novel drug delivery systems having multiple perforations wherein drugs can be housed to offer programmable release [31]. With the potential of forming inclusion and non-inclusion complexes with drugs, cyclodextrin based NS are defined as hyper cross linked supramolecular architectures that offer a plethora of opportunities to be used in drug delivery applications [32]. This detailed review crisply shows an insight into the advantages and applications of NS approach in targeted drug delivery, which successfully tames the problems such as insolubility, sensitivity, stability, toxicity and permeability issues. Figure 3 illustrates the schematic representation of the advantages of nanosponges in novel drug delivery while Figure 4 demonstrates the wide applications of nanosponge approach. Various market formulations have showing enormous promising results in terms of their efficacy, safety and stability by adapting the NS approach and Table 1 gives an overview of some examples of some formulations using NS approach. Additionally, intensive literature review reveales the prominent position of NSs in the area of nanomedicine aided drug delivery systems and have gained tremendous attention due to the ability to host various kinds of drugs and show desirable properties in terms of safety and efficacy. The list of literature or research projects involving NSs in healthcare domain, over the years is articulated in Table 2.

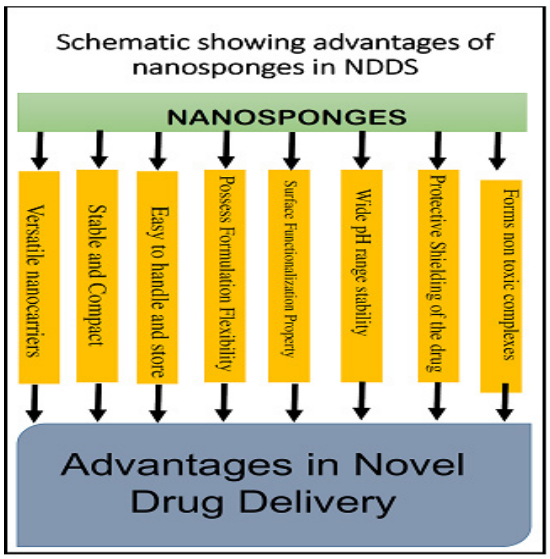

Figure 3) *Schematic representation of the advantages of nanosponges in novel drug delivery*

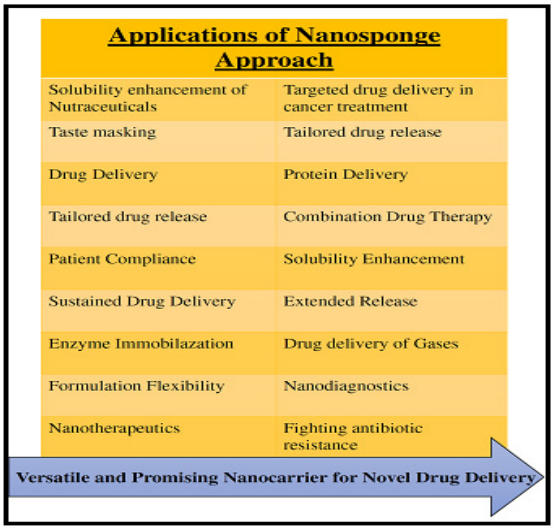

Figure 4) *Applications of nanosponge approach*

TABLE 1
List of some formulations using Nanosponge Approach

Sr. No	Drug	Category	Formulation	Polymer / Cross Linker
1	Gabapentin	Anti-Epileptic	Pediatric-Dry Suspension	β-CD/DPC
2	Paclitaxel, Camptothecin	Anti-Cancer	Tablet	β-CD
3	Econazole Nitrate	Antifungal	Hydrogel (Topical)	β-CD/DPC
4	Acyclovir	Antiviral	Tablet (Oral)	Carboxylated NS
5	Oxygen	Oxygen Delivery Systems	Gas Delivery Systems	Carbonyldiimidazole
6	Fluconazole	Antifungal	Hydrogel (Topical)	β-CD/DPC
7	Voriconazole	Antifungal	Tablet (Oral)	β-CD/DPC
8	Rilpivrine	Anti-HIV	Tablet (Oral)	β-CD/DPC
9	Sage Essential Oil	Anti-Diabetic	Nanoemulsion	β-CD/NDCA
10	Curcumin	Anti-Cancer	Tablet (Oral)	β-CD/DPC; PMDA
11	Ferulic Acid	Anti-Cancer	Tablet (Oral)	β-CD/DPC
12	Ellagic Acid	Anti-Cancer	Tablet (Oral)	β-CD/DMC
13	Doxorubicin	Anti-Cancer	Tablet (Oral)	β-CD/CDI
14	Ibuprofen	Antipyretic	Tablet (Oral)	β-CD/EDTA

Extensive literature review suggests significant contribution of NSs in the field of novel drug delivery. The multitude of advantages and applications this nanocarrier offers is indeed noteworthy of documentation and research. NS embark a promising and fruitful future in the field of nanotechnology aided novel drug delivery. The following literature illustrates the applications of this novel nanocarrier in novel drug delivery and healthcare domain.

Nanosponges in modulating drug release

The commercially available conventional drug delivery systems have a major drawback of frequent drug administration which is not patient compliant. To overcome this, the NS approach is adopted which helps to overcome this drawback by retaining the drug and releasing it slowly over time.

Nanosponges in enhancing the solubility and increasing the shelf life of nutraceuticals

Resveratrol is a potent polyphenolic phytoalexin of plant origin using in treatment of human skin infections. The low shelf life of this natural origin drug was enhanced by formulating it into a Resveratrol-NS complex [33]. *Curcumin*, another potent nutraceutical, having potent anti-tumor activities has limited applications due to its low solubility and susceptibility to degrade fast. *Curcumin* loaded NS overcome these disadvantages of the native drug [34].

Nanosponges in targeted drug delivery for cancer treatment

The main challenge in treatment of cancerous tumors is to target the drug only to the cancerous cells and not harm the normal cells [35]. The design of nanocarriers as a strategy for the delivery of anti-cancer drugs provides a promising platform to overcome some limitations of current clinical treatments and to achieve targeted release specifically into the tumor tissues.

TABLE 2
List of literature or research projects involving nanosponges in healthcare domain over the years

Year	Drug	Indication
2021	Dexibuprofen	Pain Reliever
	Econazole Nitrate	Topical Hydrogel for Skin Ailments
	Lapatinib	Breast Cancer and Solid Cancer
	Piperine	Therapeutic Agent
	Thyme Essential Oil	Anti-bacterial , Antioxidant
2020	Carboplatin	Anti-Cancer
	Rheumatic Arthritis	Methotrexate
	Breast Tumor	Doxorubicin
	Febuxostat	Gout
	Artemether and Lumefantrine	Antimalarial
	Sulfamethoxazole	Anti-Bacterial
2019	Bortezomib	Anticancer
	Ferulic Acid	Anticancer
	Cinnamon Oil	Anti-Bacterial Agent In Packaging
	Curcumin	Herbal Remedy For Cancer
	Paliperidone	Antipsychotic Drug
2018	Imatinib Mesylate	Anti-cancer
	Naproxen	Pain Relief
	Norfloxa	Anti-Bacterial
	Rilpivirine	Anti-HIV
	Ellagic Acid	Antioxidant, Anticancer
2017	Curcumin	Anticancer
	Naproxen	Inflammatio
	Nifedipine	Antihypertensive
	Ibuprofen	Analgesic, Antipyretic
	Chrysin	Anti-tumour, Antioxidant
2010 to 2016	Cefadroxil	Antibcterial
	Gabapectin	Partial Seizers
	Isonizid	HIV
	Quercetin	Antioxidant
	Camptothecin	Anti-cancer
	Paclitaxel	Anti-cancer
	Rutin, Phloridzin and Chlorogenic Acid	Anti-cancer, Anti-diabetic, Anti-obesity
	Meloxicam	Anti-Arthritic

Nanosponges in taste masking

Bitter taste was an issue faced with pediatric oral liquid dosage form of Griseofulvin which was overcome using NS approach. Additionally, Gabapectin, a well-known anti-epileptic drug is not preferred due to drawbacks of bitter taste, short biological half-life and compromised bioavailability [36]. Therefore, to overcome the limitations of this drug NS-based pediatric-controlled release dry suspension of Gabapentin was formulated.

Nanosponges in tailored drug release

The dosage forms formulated by altering the drug absorption or the site of drug release in order to satisfy predetermined clinical objectives are termed as tailored release dosage forms. NS approach has emerged as a promising tool in the development of tailored release dosage forms. Literature reveals that the issue of dissolution rate limited bioavailability of BCS class II drug Telmisartan was overcome using NS approach [37].

Nanosponges in combination drug therapy

Combination therapy is defined as the co-administration of two or more drugs to improve a therapeutic effect as compared to that of a single drug administration. The main purpose of this approach is to witness a synergistic effect. One classic example of this approach is targeted NSs for the co-administration of paclitaxel and camptothecin wherein tumor targeting peptides enhance targeting and significantly reduces tumor growth in an in vivo lung cancer model [38]. Camptothecin, a yet another potent anti-tumor drug molecule, is a highly unstable and hence carbonate β-cyclodextrin NSs of this shall be ideal to enhance the efficacy of this combination [39].

Nanosponges in solubility enhancement

The solubility issues are a major obstacle in the process of formulation development. One such poorly soluble BCS Class II drug is Itraconazole, whose issue of compromised solubility was sorted by loading it onto NS of β-CD cross-linked with carbonate bonds. Hence, NS approach is a very useful solubility enhancement tool [40].

Nanosponges in patient compliance

Versatile dosage forms like topical, parenteral, aerosol, tablet and capsules can be formulated using NS approach.

Nanosponges in shielding the drug from degradation in GIT

Prevention of enzymatic breakdown of the drugs in gastrointestinal tract is a challenging barrier in formulation development. This obstacle is overcome by NS approach. Cyclodextrin based NS will increase the life of the drug in gastrointestinal tract and also reduce the irritation caused by drugs, as they enclose the drug inside the pocket of the polymer [41].

Nanosponges in formation of non-toxic, stable, non-mutagenic complexes

NSs form inclusion and non-inclusion complexes with drug molecules of different polarities, enzymes, proteins, peptides and macromolecules and offer an interesting complexation potential with both hydrophobic and hydrophilic compounds. This host-guest interaction provides enhancement in stability, solubility and sometimes in membrane permeability and also facilitates the formation of stable, non-allergic and non-toxic complexes.

Nanosponges- A breakthrough approach in sustained drug delivery

The drug delivery system which allows the delivery of a drug molecule at a programmed rate to prolong the time period of drug delivery and avoid frequent dosing is termed as sustained drug delivery system. A potent antiviral agent, Acyclovir, faces problems owing to its slow and incomplete absorption in the gastrointestinal tract. Neither the parenteral nor the oral ingestion of its marketed formulation is able to achieve suitable concentrations of Acyclovir reaching target sites [42]. This issue was resolved by formulating carboxylated cyclodextrin based NS carrying carboxylic groups within their structure as efficient Acyclovir carriers.

Nanosponges in extended release upto 12 hours to 24 hours

Lansoprazole is a proton pump inhibitor with compromised solubility and stability. The frequent administration is of Lansoprazole is waived through its NS loaded extended-release tablets. The extended-release formulations offer slow and steady drug release over an extended period of time to reduce the frequency of dosing, which is a patient compliant attribute. Thus, by altering the polymer: cross linker ratio, the release of Lansoprazole can be extended [43].

Nanosponges in incorporation of enzymes, proteins, antibodies and insoluble liquids

It is observed that during long term storage macromolecules such as proteins face major stability issues. Novel swellable cyclodextrin based NS were prepared by crosslinking β-CDs with either 2,2-bis-acrylamidoacetic acid or a short polyamido-amine chain derived from 2,2-bis-acrylamidoacetic acid and 2-methyl piperazine respectively. The synthesized β-CD based poly (amidoamine) - NS were found to be stable at temperatures up to 300°C and demonstrated enhanced complexation efficiency [44].

Nanosponges in extended stability over high temperatures and pH range

Nanotechnology aided NS are encapsulating type nanocarriers which are prepared using biodegradable polymer and hence are biocompatible and biologically safe. They enmesh drug within their cavities and enhance the stability, solubility and bioavailability of it. A remarkable improvement in the side effect profile of the drug is also noted due to NS approach.

Nanosponges can be modified into desired size and polarity by varying the polymer: cross linker ratio

The NS are synthesized using a polymer and a cross linker in a specific ratio. The cross linkers are tiny hook like structures which permit NS to adhere preferentially to the target site.

Nanosponges as a carrier for gaseous delivery systems

Gases like oxygen essentially play an important role in the medical and healthcare domain. But delivery of oxygen in a suitable form is indeed challenging. The application of NS approach in the delivery of oxygen via topical route is explored, which had the caliber to entrap and liberate oxygen periodically over a specified time period [45]. Additionally, Carbondioxide NSs can be used for various biomedical applications [46].

Application of nanosponges in enzyme immobilization

Immobilization is a technique which improves many properties of enzymes like performance in organic solvents, pH tolerance, heat stability or functional stability. Enzyme immobilization is a technique which resists the change in temperature or pH of the enzyme by preferentially binding it to an inert support. Cyclodextin based NS have been explored for adsorption of certain enzymes. It is reported in literature that *Pseudomonas* fluorescens lipase is adsorbed on cyclodextrin based carbonate NS yielding enhanced structural and functional stabilization [47].

Formulation flexibility

NSs can be formulated as topical, pulmonary, ocular preparations. One such example is a polymeric hydrogel NS formulation of Econazole Nitrate to increase its retention time and controlling its release upto 12 hours [48]. Pulmonary drug delivery system involves drug administration through the respiratory tract in the form of aerosol. NS approach shows promising applications in this domain too [49]. A cyclodextrin-based NS formulation with potential to improve corneal permeation was used as drug carrier in topical ocular drug delivery. Additionally, Miconazole nitrate loaded NSs were formulated into vaginal gels [50, 51].

Application of nanosponges in nanotherapeutics

Nanotechnology has revolutionized the healthcare strategies and aims to have a tremendous influence to offer better medical facilities. Nanotherapeutics is a branch of nanotechnology in medicine dealing with the design, fabrication, regulation and application of therapeutic drugs and devices having dimensions in nano-range. Mn3O4 Nanoerythrocyte T7 NSs can regulate oxygen and scavenge free radicles in the event of ischemia (heart stroke). Hence such engineered NSs are the prominent examples of NSs in nanotherapeutics [52].

Application of nanosponges in nanodiagnostics

NSs are useful diagnostic aids and have profound applications in the detection of various diseases. They selectively absorb biomarkers for the diagnosis of various diseases and are used to carry fluorescent dyes, which act as diagnostic aids [53].

Application of nanosponges as protective agents

NSs are important shielding tools against degradation from light (photo degradation). The gamma oryzanol can be encapsulated using NS approach to prevent photo degradation [54].

Application of nanosponges in fighting antibiotic resistance

Membrane coated NSs fight antibiotic resistance. They can be used to trap and remove toxins from blood [55].

Patent on nanosponges for novel drug delivery applications

In addition to highlighting the advantages and applications of NS in novel drug delivery, this review embraces the inventions disclosed in the patents on NSs. It gives detailed information of the inventions related to NSs application in the field of novel drug-delivery which is summarized in Table 3. Based on extensive studies it was observed that NSs have been useful in a variety of applications ranging from controlled drug delivery, delivery of low soluble drugs, vaccines, enzymes, proteins etc. Variety of biodegradable and organic/inorganic polymers can be used for the synthesis of NSs in different ratios for efficacious drug delivery applications [56]. In pharmaceutical technology, these structured complexes can be used to elevate the dissolution rate, solubility and stability of drugs, to mask unpleasant flavors or to convert liquid substances to solids, etc. The Table 3 crisply outlines the noteworthy patented work in this domain.

CONCLUDING NOTES AND FUTURE PROSPECTS

In the light of such findings, it can be concluded that nanotechnology has been a boon to the novel drug delivery and has brought a revolutionary change in drug delivery and medical research. Cyclodextrin-based NSs are multifaceted biocompatible nanocarriers which can be produced on lab scale in a cost-effective manner. These nanocarriers offer superiority over simple polymer in terms of offering enhanced solubility, stability and release profile. They offer complexation capacity with a multitude of hydrophilic and lipophilic drugs molecules, which presents a variety of advantages as novel nanocariers. Owing to their compact size and spherical shape, NSs have the promising potential to be formulated into a wide range of dosage forms such as topical, tablets and capsules, parenteral and aerosol. Additionally due to the special features and versatile properties, NSs could be adopted for a variety of other applications for novel drug delivery. It would be interesting to explore NS aided drugs for cancer treatment as therapeutic agents and diagnostic markers. Also, areas like brain targeting issues can be answered using NS approach. Scope to develop magnetic NS for targeting drugs to diseases cells and research into this area shall be very promising in the coming future. Furthermore, the cosmaceutical and the nutraceutical sector also

TABLE 3

List of patents on nanosponges for novel drug delivery applications

Sr. No	Patent Application Number	Title of Patent
1	WO2009003656A1	Cyclodextrin-based nanosponges as a vehicle for antitumoral drugs
2	WO2012147069A1	Method for preparing dextrin nanosponges
3	WO2009149883A1	Cyclodextrin nanosponges as a carrier for biocatalysts, and in the delivery and release of enzymes, proteins, vaccines and antibodies
4	WO2019202148A1	Cross-linked starch-based polymers for drug-delivery
5	ITMI20040614A1	Nanosponges based on cyclodextrins functionalized with carboxyl groups in the synthesis and use decontamination from heavy metals and organic compounds by chromatographic separations and drug delivery
6	WO2020011197A1	Cross-linked nanoporous saccharide-based material and methods for fabrication thereof
7	KR101920284B1	Heparin nanosponge for controlled release of growth factors and method for manufacturing thereof
8	CN108703944A	Licoflavone nanosponges and its preparation proces
9	KR20190122368A	Injectable thermosponge nanoparticle-based hydrogel and its use
10	WO2019182278A1	Thermosponge nanoparticle platform for simultaneous delivery of hydrophilic and hydrophobic drugs, and use thereof
11	US8372933B2	Hyperbranched polymers based on cyclodextrins and poly (amidoamines) for the controlled release of insoluble drugs

demand formulating drugs via this approach for better performance. Finally, the manifold applications of NSs extends beyond the boundaries of drug delivery to domains of environment remediation, agriculture, biomedicine etc. and are indeed worthy of study and documenting.

CONSENT FOR PUBLICATION

The manuscript has no data which requires consent prior to publishing.

FUNDING

None.

CONFLICT OF INTEREST

The authors have no conflicts of interest that are directly relevant to the content of this review.

ACKNOWLEDGEMENTS

The support from Babaria Institute of Pharmacy, BITS Edu Campus and Ramanbhai Patel College of Pharmacy, CHARUSAT, Changa, is acknowledged.

REFERENCES

1. Kapil A, Aggarwal G, Harikumar SL. Nanotechnology in novel drug delivery system. J Drug Deliv Ther 2014; 4(5):21-8.
2. Mishra M, Kumar P, Rajawat JS, et al. Nanotechnology: revolutionizing the science of drug delivery. Curr Pharm Des 2018;24(43):5086-107.
3. Emeje MO, Obidike IC, Akpabio EI, et al. Nanotechnology in drug delivery. Recent Advances in Novel Drug Carrier Systems 2012; 69-106.
4. Bamrungsap S, Zhao Z, Chen T, et al. Nanotechnology in therapeutics: a focus on nanoparticles as a drug delivery system. Nanomedicine 2012;7(8):1253-71.
5. Farooq MA, Aquib M, Farooq A, et al. Recent progress in nanotechnology-based novel drug delivery systems in designing of cisplatin for cancer therapy: an overview. Artificial Cells, Nanomedicine, and Biotechnology 2019;47(1):1674-92.
6. Koo OM, Rubinstein I, Onyuksel H. Role of nanotechnology in targeted drug delivery and imaging: a concise review. Nanomedicine: Nanotechnology, Biology and Medicine 2005;1(3):193-212.
7. Ravichandran R. Nanotechnology-based drug delivery systems. NanoBiotechnology 2009;5(1-4):17-33.
8. Marcato PD, Durán N. New aspects of nanopharmaceutical delivery systems. Journal of Nanoscience and Nanotechnology 2008;8(5):2216-29.
9. Parhi P, Mohanty C, Sahoo SK. Nanotechnology-based combinational drug delivery: an emerging approach for cancer therapy. Drug Discovery Today 2012;17(17-18): 1044-52.
10. Cai Z, Wang Y, Zhu LJ, et al. Nanocarriers: a general strategy for enhancement of oral bioavailability of poorly absorbed or pre-systemically metabolized drugs. Current Drug Metabolism 2010;11(2):197-207.
11. Aberoumandi SM, Mohammadhosseini M, Abasi E, et al. An update on applications of nanostructured drug delivery systems in cancer therapy: a review. Artificial Cells, Nanomedicine, and Biotechnology 2017;45(6):1058-68.
12. Avila-Olias M, Pegoraro C, Battaglia G, et al. Inspired by nature: fundamentals in nanotechnology design to overcome biological barriers. Therapeutic Delivery 2013;4(1):27-43.
13. Sahoo SK, Labhasetwar V. Nanotech approaches to drug delivery and imaging. Drug Discovery Today 2003;8(24):1112-20.
14. Huang Q, Yu H, Ru Q. Bioavailability and delivery of nutraceuticals using nanotechnology. Journal of Food Science 2010;75(1):R50-R57.
15. Acosta E. Bioavailability of nanoparticles in nutrient and nutraceutical delivery. Current Opinion in Colloid & Interface Science 2009;14(1):3-15.
16. Carbone C, Cupri S, Leonardi A, et al. Lipid-based nanocarriers for drug delivery and targeting: a patent survey of methods of production and characterization. Pharmaceutical Patent Analyst 2013;2(5): 665-77.
17. Bhatia S. Nanoparticles types, classification, characterization, fabrication methods and drug delivery applications. In Natural Polymer Drug Delivery Systems 2016;33-93.
18. Patil TS, Nalawade NA, Kakade VK, et al. Nanosponges: A novel targeted drug delivery for cancer treatment. International Journal for Advance Research and Development 2017;2(4).
19. Shringirishi M, Prajapati SK, Mahor A, et al. Nanosponges: a potential nanocarrier for novel drug delivery-a review. Asian Pacific Journal of Tropical Disease 2014; 4: S519-26.
20. Trotta F, Dianzani C, Caldera F, et al. The application of nanosponges to cancer drug delivery. Expert Opinion on Drug Delivery 2014;11(6):931-41.
21. Chilajwar SV, Pednekar PP, Jadhav KR, et al. Cyclodextrin-based nanosponges: a propitious platform for enhancing drug delivery. Expert Opinion on Drug Delivery 2014;11(1):111-20.
22. Sherje AP, Dravyakar BR, Kadam D, et al. Cyclodextrin-based nanosponges: a critical review. Carbohydrate Polymers 2017;173:37-49.
23. Jeganath S, Abdelmagid KFK. A review on nanosponges-A promising novel drug delivery system. Research Journal of Pharmacy and Technology 2021;14(1):501-5.
24. Selvamuthukumar S, Anandam S, Krishnamoorthy K, et al. Nanosponges: A novel class of drug delivery system-review. Journal of Pharmacy & Pharmaceutical Sciences 2012; 15(1): 103-111.
25. Tejashri G, Amrita B, Darshana J. Cyclodextrin based nanosponges for pharmaceutical use: A review. Acta Pharmaceutica 2013;63(3):335-58.
26. Ahmed RZ, Patil G, Zaheer Z. Nanosponges–a completely new nano-horizon: pharmaceutical applications and recent advances. Drug Development and Industrial Pharmacy 2013;39(9):1263-72.
27. Anandam S, Selvamuthukumar S. Fabrication of cyclodextrin nanosponges for quercetin delivery: physicochemical characterization, photostability, and antioxidant effects. Journal of Materials Science 2014;49(23):8140-53.
28. Pushpalatha R, Selvamuthukumar S, Kilimozhi D. Hierarchy analysis of different cross-linkers used for the preparation of cross-linked cyclodextrin as drug nanocarriers. Chemical Engineering Communications 2018;205(6):759-71.
29. Venuti V, Rossi B, Mele A, et al. Tuning structural parameters for the optimization of drug delivery performance of cyclodextrin-based nanosponges. Expert Opinion on Drug Delivery. 2017;14(3):331-40.
30. Mura P. Analytical techniques for characterization of cyclodextrin complexes in the solid state: A review. Journal of Pharmaceutical and Biomedical Analysis. 2015;113:226-38.
31. Waghmare SG, Nikhade RR, Satish D, et al. Nanosponges: a novel approach for controlled release drug delivery system. International Journal of Pharmacy and Pharmaceutical Research. 2017;9(3):101-11.
32. Indira B, Bolisetti SS, Samrat C, et al. Nanosponges: a new era in drug delivery: review. Journal of Pharmacy Research 2012;5(12):5293-5296.
33. Ansari KA, Vavia PR, Trotta F, et al. Cyclodextrin-based nanosponges for delivery of resveratrol: in vitro characterisation, stability, cytotoxicity and permeation study. Aaps Pharmscitech. 2011;12(1):279-86.
34. Darandale SS, Vavia PR. Cyclodextrin-based nanosponges of curcumin: formulation and physicochemical characterization. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2013;75(3-4):315-22.
35. Kamble M, Zaheer Z, Mokale S, et al. Formulation optimization and biopharmaceutical evaluation of imatinib mesylate loaded β-cyclodextrin nanosponges. Pharmaceutical Nanotechnology 2019;7(5):343-61.
36. Rao MR, Bhingole RC. Nanosponge-based pediatric-controlled release dry suspension of Gabapentin for reconstitution. Drug Development and Industrial Pharmacy 2015;41(12):2029-36.
37. Rao M, Bajaj A, Khole I, et al. In vitro and in vivo evaluation of β-cyclodextrin-based nanosponges of telmisartan. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2013;77(1-4):135-45.
38. Hariri G, Edwards AD, Merrill TBet al. Sequential targeted delivery of paclitaxel and camptothecin using a cross-linked "nanosponge" network for lung cancer chemotherapy. Molecular Pharmaceutics 2014;11(1):265-75.
39. Swaminathan S, Pastero L, Serpe L, et al. Cyclodextrin-based nanosponges encapsulating camptothecin: physicochemical characterization, stability and cytotoxicity. European Journal of Pharmaceutics and Biopharmaceutics. 2010;74(2):193-201.

40. Swaminathan S, Vavia PR, Trotta F, et al. Formulation of betacyclodextrin based nanosponges of itraconazole. Journal of Inclusion Phenomena and Macrocyclic Chemistry 2007;57(1):89-94.

41. Zainuddin R, Zaheer Z, Sangshetti JN, et al. Enhancement of oral bioavailability of anti-HIV drug rilpivirine HCl through nanosponge formulation. Drug Development and Industrial Pharmacy. 2017;43(12):2076-84.

42. Lembo D, Swaminathan S, Donalisio M, et al. Encapsulation of Acyclovir in new carboxylated cyclodextrin-based nanosponges improves the agent's antiviral efficacy. International Journal of Pharmaceutics 2013;443(1-2):262-72.

43. Penjuri SCB, Ravouru N, Damineni S, et al. Formulation and evaluation of lansoprazole loaded Nanosponges. Turk J Pharm Sci. 2016;13(3):304-10.

44. Hayiyana Z, Choonara Y, Makgotloe A, et al. Ester-based hydrophilic cyclodextrin nanosponges for topical ocular drug delivery. Current Pharmaceutical Design. 2016;22(46):6988-97.

45. Cavalli R, Akhter AK, Bisazza A, et al. Nanosponge formulations as oxygen delivery systems. International Journal of Pharmaceutics. 2010;402(1-2):254-57.

46. Trotta F, Cavalli R, Martina K, et al. Cyclodextrin nanosponges as effective gas carriers. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2011;71(1):189-94.

47. Boscolo B, Trotta F, Ghibaudi E. High catalytic performances of Pseudomonas fluorescens lipase adsorbed on a new type of cyclodextrin-based nanosponges. Journal of Molecular Catalysis B: Enzymatic. 2010; 62(2):155-61.

48. Sharma R, Pathak K. Polymeric nanosponges as an alternative carrier for improved retention of econazole nitrate onto the skin through topical hydrogel formulation. Pharmaceutical Development and Technology. 2011;16(4):367-76.

49. Shivani S, Poladi KK. Nanosponges-novel emerging drug delivery system: A review. International Journal of Pharmaceutical Sciences and Research. 2015;6(2):529.

50. Kumar PS, Hematheerthani N, Ratna JV, et al. Design and characterization of miconazole nitrate loaded nanosponges containing vaginal gels. Int J Pharm Ana Res. 2016;5(3):410-7.

51. Abass MM, Rajab NA. Preparation and characterization of etodolac as a topical nanosponges hydrogel. Iraqi Journal of Pharmaceutical Sciences. 2019;28(1):64-74.

52. Shi J, Yu W, Xu L, et al. Bioinspired nanosponge for salvaging ischemic stroke via free radical scavenging and self-adapted oxygen regulating. Nano Letters 2019;20(1):780-9.

53. Osmani AM, Bhosale R, Hani U, et al. Cyclodextrin based nanosponges: impending carters in drug delivery and nanotherapeutics. Current Drug Therapy. 2015;10(1):3-19.

54. Sapino S, Carlotti ME, Cavalli R, et al. Photochemical and antioxidant properties of gamma-oryzanol in beta-cyclodextrin-based nanosponges. Journal of Inclusion Phenomena and Macrocyclic Chemistry. 2013;75(1-2):69-76.

55. Liu Y, Liao Y, Li P, et al. Cross-linked pillar [6] arene nanosponges fabricated by the use of a supra-amphiphilic template: cargo encapsulation and overcoming multidrug resistance. ACS Applied Materials & Interfaces 2020;12(7):7974-83.

56. Pawar S, Shende P. A comprehensive patent review on β-cyclodextrin cross-linked nanosponges for multiple applications. Recent Patents on Nanotechnology 2020;14(1):75-89.